Current Chemotherapy of Small Cell Lung Cancer*

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Since the advent of effective cytotoxic combinations in the early 1970s, results from chemotherapy for small cell lung cancer have improved very little. Maintenance chemotherapy appears of no benefit. Although attractive theoretically, "non-cross-resistant" combinations may not yet exist, and most data do not support alternating 1 regimen with another. Anticoagulant therapy with warfarin probably does not have a meaningful impact on survival, at least in extensive stage disease. To date the addition of VP-16, an active new agent, has not produced improvement in survival over earlier programs. The most promising leads to date involve dose escalation, especially with cyclophosphamide. Moderate "outpatient" escalation in limited disease induction therapy produced survival benefit in a randomized trial, and several studies indicate that the incidence of complete response can be increased by more intensive, inpatient "consolidation" with cyclophosphamide with or without other drugs after the induction period. Some form of local therapy, however, will be necessary to control disease in the chest, even with maximal dose intensification.

In the 1970s, single-agent cyclophosphamide was replaced by 3- and 4-drug combinations for the initial chemotherapy of small cell lung cancer, and the use of combined modalities replaced radiation therapy alone as a "standard" approach to limited disease. Since then, attempts to develop improved systemic treatment have involved several themes: (1) "maintenance" chemotherapy after the induction period, with the same or different drugs given at lower doses in an attempt to prolong remission duration; (2) dose escalation beyond those previously employed, either as initial induction or in an attempt to "consolidate" and prolong remissions; (3) "late intensification" (reinduction) after several months in remission, with higher pulsed doses of the same drugs used for induction; (4) the use of alternating combinations that are postulated to be "non-cross-resistant," first on an intuitive basis and more recently with mathematical support as outlined in the Goldie-Coldman hypothesis; (5) the use of additive anticoagulation with agents such as warfarin; and (6) continued empiric exploration of new agents and combinations. Each of these themes will be reviewed and some tentative conclusions suggested about their future.

Maintenance chemotherapy is of proved value in treatment of childhood acute lymphocytic leukemia but has fallen from favor in the treatment of most chemosensitive adult malignancies with the potential for cure. Two randomized trials have addressed the issue in small cell lung cancer. In the first, reported by Maurer et al1 for the Cancer and Leukemia Group B, patients who achieved complete remission had prolonged survival, but no effect on response duration could be demonstrated from the continued administration of intermittent cyclophosphamide on an outpatient basis. The second, reported by Woold and Levi,4 randomized patients after several cycles of induction chemotherapy with cis-platin and VP-16 to receive or not receive cyclophosphamide, doxorubicin (Adriamycin), and vincristine, on an intensive, intermittent schedule as outpatients.4 No benefit was demonstrated. Nonrandomized comparisons of earlier experience that included maintenance chemotherapy with later trials in which it was omitted were reported by Natale et al6 from the Memorial group and by Feld et al:7 neither suggested any benefit from maintenance. Although it is still commonly employed in "conventional" practice, most new investigative programs of treatment for this disease do not include maintenance chemotherapy.

Dose escalation is supported by a solid, virtually uniform experience in experimental tumor systems, which indicates that "more is better" to the limits of tolerable toxicity,8 and by some, but not all, clinical trials in other human cancers.9 Controlled trials of moderately intensive dose escalation originated with the report of Cohen et al,10 using the combination of cyclophosphamide, methotrexate, and CCNU (CMC). This trial appeared to show clear-cut benefit from an increase in cyclophosphamide (Cytoxan) dose of 500-1,000 mg/m² and an increase in the dose of CCNU from 50 to 100 mg/m². The Eastern Cooperative Group was stimulated to carry out a "confirmatory" trial, although the design for dose escalation was altered somewhat.11 The schema for the trial, and the most recent comparisons from it reported by Vogl and Mehta12 for response and survival, are shown in Table 1. Of particular note is the statistically significant prolongation

<table>
<thead>
<tr>
<th>Intensive</th>
<th>Standard</th>
<th>p Value</th>
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<tbody>
<tr>
<td>1,500/m²</td>
<td>Cyclophosphamide</td>
<td>700/m²</td>
</tr>
<tr>
<td>70/m²</td>
<td>CCNU</td>
<td>70/m²</td>
</tr>
<tr>
<td>15/m²×2/wk</td>
<td>Methotrexate</td>
<td>15/m²×2/wk</td>
</tr>
<tr>
<td>64%</td>
<td>Response to induction</td>
<td>54%</td>
</tr>
<tr>
<td>29 wk</td>
<td>Time to progression</td>
<td>24 wk</td>
</tr>
<tr>
<td>41 wk</td>
<td>Median survival time</td>
<td>36 wk</td>
</tr>
<tr>
<td>56 wk</td>
<td>Median survival time</td>
<td>42 wk</td>
</tr>
<tr>
<td>34 wk</td>
<td>Median survival time, limited disease</td>
<td>31 wk</td>
</tr>
</tbody>
</table>

| Extensive disease |

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in survival, accounted for primarily by an effect in limited disease patients. Toxicity from this degree of dose-escalation was, however, formidable enough to prevent its routine adoption on an outpatient basis: 53% of the patients on the “intensive” induction program had complications rated as “life-threatening” and 4% had drug-related deaths, compared to 7% and 1%, respectively, at the “standard” dose. A third controlled trial was recently reported by the Albany group.\textsuperscript{29} In it, the 3-drug combination used was cyclophosphamide (at 750 vs 2,000 mg/m\(^2\)), methyl-CCNU (at 75 vs 100 mg/m\(^2\)), and vincristine (dose constant at 2 mg). Too small for statistically significant conclusions, the trial is of interest because of a higher complete response rate on the intensive program and apparent improvement in median survival of the complete responders (22 vs 12 months). The Southwest Oncology Group (SWOG) has performed sequential studies of the combination of cyclophosphamide, Adriamycin, and vincristine (CAV) in patients with extensive small cell lung cancer, with no apparent improvement in complete response rate or survival and somewhat more toxicity when the doses of cyclophosphamide and Adriamycin were intensified from 50/750 to 60/1,000 mg/m\(^2\), respectively.\textsuperscript{10} However, the degree of cyclophosphamide escalation was less than in the ECOG trial.

A more radical approach to dose escalation involves the administration of cytotoxic drugs at doses that require hospitalization, intensive supportive care, and even, in some instances, the infusion of previously stored autologous bone marrow. For cyclophosphamide in particular, there is substantial evidence from uncontrolled trials that such escalation (5-10 times the usual dose) produces a dramatic increase in response rates. Given at doses in the range of 1,000 mg/m\(^2\) (about 40 mg/kg), cyclophosphamide produces complete or partial responses in about 30% of patients.\textsuperscript{11} Ettinger et al\textsuperscript{12} reported that a dose of 60 mg/kg/day for 2 consecutive days produced responses in 70% of patients.\textsuperscript{13} Various studies have shown that most of these responses are durable and that patients may achieve complete remissions at relatively low dose intensity. Patients with limited disease, who are considered candidates for intensive induction chemotherapy, are candidates for such approaches.

“Late intensification” may be considered a variation on the theme of dose-response, the concept being that achieving an additional 1 or 2 logs of cell kill may be much more important if the tumor burden has already been reduced by effective induction. The Southwest Oncology Group reported on the outcome of a randomized trial in extensive disease in which patients who remained progression-free at 24 weeks were given either continued monthly, low-dose pulses of maintenance chemotherapy with cyclophosphamide and VP-16, or a single cycle of their initial induction chemotherapy at 24 weeks and again at 1 year on study, with similar maintenance chemotherapy in the interim.\textsuperscript{15} Although there was no overall difference between the randomized groups, there was a statistically significant survival advantage for the subgroup of complete responders among those who received late intensification. Since the chemotherapy was the same as that originally used for induction, this observation would further imply that uniform somatic mutation to clinical resistance is not a ubiquitous feature of residual tumor, even after several months. There was no evidence that this effect on the small subpopulation of complete responders translated into survival benefit for extensive stage patients as a whole compared with previous experience in SWOG. However, in a separate study for patients with limited stage disease, which was carried out by SWOG at the same time and in which late intensification was administered to all responders at 24 weeks and 1 year, a survival advantage is apparent by comparison to previous historical controls. Whether this was in fact due to the late intensification can be verified only by a prospective, randomized study.

Analogous to the more radical approaches to induction dose escalation, several investigators have now examined the feasibility of very high-dose, inpatient intensification, usually as “consolidation” shortly after the induction period. In 1983 Smith et al\textsuperscript{16} reported on the use of high-dose cyclophosphamide (7,000 mg/m\(^2\)), with or without autologous marrow infusion, at completion of 4 “conventional” induction cycles with VP-16, Adriamycin, and vincristine. Of 15 patients with partial response to initial chemotherapy, 13 reported improved response (4 to complete response); however, the median response duration in these patients after consolidation was only 10 weeks, with 11 of 13 “improved” patients relapsing, mainly at the primary site. No local therapy was used in this study. Spitzer et al\textsuperscript{17} reported in 1984 on the use of cyclophosphamide at 4.5 g/m\(^2\) together with VP-16 at 600 mg/m\(^2\), with or without vincristine, followed by autologous marrow infusion as an intensification program after 3 cycles of “standard” induction therapy. This was followed by brain and chest irradiation. Of 29 patients treated, 21 achieved complete remission, and 11 of these did so after intensification. Definitive follow-up on this study is not yet available. Perhaps the most provocative study of “radical” intensification yet reported was presented by a Belgian group in 1985.\textsuperscript{18} In this randomized trial, all patients received 3 cycles of CAV plus methotrexate, followed by 1 cycle of cis-platin plus VP-16 with concomitant, elective whole brain irradiation. The control group then received an additional course of standard dose chemotherapy, while the intensification group received cyclophosphamide 1.5 g/m\(^2\)/day \(\times 4\), BCNU in a single dose of 300 mg/m\(^2\), and VP-16 125 mg/m\(^2\)/day \(\times 4\), followed by infusion of previously stored autologous marrow. For patients with limited-stage disease, there was a statistically significant advantage in disease-free survival for the intensified group (median of 40 vs 8 weeks after randomization) and median survival was improved (104 vs 58 weeks). Six of 7 partial
responders with limited disease, and 2 of 3 partial responders with extensive disease converted to complete response status after intensification. No local therapy was delivered to the primary site, and 11/12 reported relapses were in the chest.

An even more widely explored investigational approach than does intensification has been the use of intentionally sequenced, alternating combinations that are putatively non-cross-resistant. Table 2 briefly reviews the results of six randomized trials reported to date that were based on this concept.

The trial reported recently by Daniels et al.²⁶ bears further analysis, since it is the only unrefuted "positive" result yet reported with this approach. The basic trial design differs from other randomized trials in that the initial component of the "alternating" approach is a different regimen (VAM) from the control (POCC), raising the possibility that VAM is simply a better induction program. Secondly, VAM was actually repeated for 3 induction cycles in the "alternating" arm before patients received POCC, after which the regimens were alternated. Most available evidence from chemotherapy trials in small cell lung cancer indicates that maximal response is achieved (at standard doses) in the first 3 cycles. However, as shown in Table 3, the overall and complete response rate reported after three cycles of VAM or 2 cycles of POCC was actually identical, with a doubling in complete response rate after VAM-POCC that resulted in a statistically significant higher rate of ultimate complete response than after POCC-POCC (in extensive stage only). Survival and time to progression are shown from this trial in Table 4. Again, the significant advantage is confined to patients with extensive-stage disease. This is disturbing, since it runs counter to the intuitive expectation that patients with lesser tumor burden should be those in whom the benefit of any scheduling manipulation is most obvious. The authors attribute the lack of demonstrated benefit in limited-stage disease to the fact that, in this group, administration of the POCC-VAM alternating sequence was delayed to allow delivery of chest irradiation.

The NCI-Canada trial²⁸ is also "different" in its design in that regimens were actually alternated in both arms. In the "control" arm, all patients went on to receive 3 cycles of cisplatin plus VP-16 if they remained in this study after 3 cycles of CAV. In the "experimental" arm, the regimens were changed to an alternating approach after the first cycle. In any event, preliminary analysis demonstrated identical response rates, a median survival of 14 months in both arms, and a projected 2-year survival of 20%. The survival figures appear similar to historical controls for CAV alone. Similar results are apparent from a recently closed trial by the SWOG, comparing repetitive cycles of CAV plus VP-16 with the rapid alternation of cisplatin plus VP-16 and CAV (Goodman G, unpublished data). Both these trials involved only patients with limited stage disease.

Anticoagulation with warfarin was originally attempted based on the hypothesis that it might inhibit the propagation of further growth of metastases. Recently it was suggested that warfarin may exert cytotoxic effects independently.²⁴

### Table 2—Results of Randomized Trials with Alternating Drug Combinations

<table>
<thead>
<tr>
<th>Investigator (Group) and Reference</th>
<th>Regimens Compared</th>
<th>Outcome and Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al²⁵ (ECOG)</td>
<td>CMC-CMC vs CMC-VAP</td>
<td>Positive for alternating approach</td>
</tr>
<tr>
<td>Vogl and Mehta²⁶ (ECOG)</td>
<td>CMC-CMC vs CMC-VAP</td>
<td>No difference</td>
</tr>
<tr>
<td>Livingston et al²³ (SWOG)</td>
<td>VMV-VAC vs VMV-VMV</td>
<td>No difference—extensive disease only</td>
</tr>
<tr>
<td>Østergaard et al²² (Denmark)</td>
<td>CMCV-CMCA vs CMCV-AE</td>
<td>No statistical difference—long-term survivors only in alternating group—extensive disease only</td>
</tr>
<tr>
<td>Daniels et al²⁷ (NCG)</td>
<td>POCC-POCC vs VAM×3→POCC-VAM</td>
<td>Positive for alternating approach—seen in extensive stage only</td>
</tr>
<tr>
<td>Feld et al²⁸ (Canada-NCI)</td>
<td>CAV×3→cisplatin+VP-16×3 vs CAV-cisplatin+VP-16</td>
<td>No difference—limited disease only</td>
</tr>
</tbody>
</table>

### Table 3—NCOG Trial—Response Rates

<table>
<thead>
<tr>
<th>Initial</th>
<th>VAM × 3</th>
<th>POCC × 2</th>
<th>VAM-POCC</th>
<th>POCC</th>
</tr>
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<tr>
<td>All patients</td>
<td>19 (CR%)</td>
<td>21</td>
<td>42 (CR%)</td>
<td>31</td>
</tr>
<tr>
<td>Limited disease</td>
<td>45 (R%)</td>
<td>49</td>
<td>60 (R%)</td>
<td>61</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>53</td>
<td>55</td>
<td>20*</td>
<td></td>
</tr>
<tr>
<td>Extensive disease</td>
<td>63</td>
<td>R(%)</td>
<td>53</td>
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</tr>
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</table>

*p = .03

### Table 4—NCOG Trial—Survival and Time to Progression

<table>
<thead>
<tr>
<th></th>
<th>MTP (mo)</th>
<th>MST (mo)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Limited</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Extensive</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

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Earlier, small randomized trials of chemotherapy with or without warfarin reported conflicting results. The Cancer and Leukemia Group B has now completed a large, prospective randomized trial, testing two concepts in extensive disease: (1) comparison of "control" induction with MACC (methotrexate, Adriamycin, CCNU, and cyclophosphamide) and a potentially "non-cross-resistant" arm, MEPH/MACC (where MEPH is mitomycin C, etoposide, cis-platin and hexamethylmelamine; and (2) comparison of MACC plus or minus warfarin, given in a standard fashion to prolong the prothrombin time difference to 2 to 3 times control values. The results of this trial are summarized in Table 5. Although a significant response rate difference in a 3-way comparison apparently exists in favor of the warfarin-treated patients, no evidence of statistical benefit exists at this time for time to progression or survival. MACC and MEPH-MACC appear to be identical.

A final topic of the past 10 years in small cell clinical research has been the attempt to discover new drugs, or drug combinations, which are more effective than "standard programs like CAV or CMC. The new agent of clear activity identified during that time is VP-16 (etoposide), which has single-agent activity comparable to or greater than cyclophosphamide. Several randomized trials have dealt with the straightforward issue of whether simply adding VP-16 to a standard regimen improves results. The Central Pennsylvania Oncology Group (CPOG) performed such a randomized study in 82 patients, with a significantly higher rate of complete response in extensive-stage and higher overall response rates in limited disease when VP-16 was added. There was, however, no effect on response duration or survival, and the VP-16-containing regimen was more toxic. The Piedmont Oncology Group studied a slightly more aggressive CAV program, to which VP-16 was added at 60 mg/m^2 day × 5 in the experimental arm. The most recent reported analysis of this study demonstrates a highly significant response rate advantage for the VP-16-containing arm (84% vs 40%), and an advantage in complete response rate as well (34 vs 14%). Time to progression was significantly longer as well, but survival apparently not different (median 7 vs 9 months, p = 0.13). Again, more toxicity was observed when VP-16 was added. In an attempt to avoid the problem of discrepant results related to intensity of therapy rather than its components, the Southeast Group compared CAV with or without VP-16, but at doses that produced essentially equivalent toxicity in the 2 arms: the results were identical.

The "new" combination of greatest interest has unquestionably been cis-platin plus VP-16. The Memorial-Sloan Kettering group initially reported and subsequently confirmed that this 2-drug combination is at least as active as any other initial induction regimen. Although no prospective, randomized comparison exists to VP-16 alone, the combination appears to be more active. Whether this represents synergism or an additive effect is uncertain, since cis-platin itself has not been evaluated as first-line treatment alone. That cis-platin plus VP-16 represented the long-sought-after "truly" non-cross-resistant regimen was suggested by the results of several pilot studies which indicated response rates of 50-70% in the "salvage" setting, after disease progression in a setting of prior chemotherapy. However, the activity of this combination as "salvage" has not been confirmed in cooperative group trials by the Cancer and Leukemia Group B and the SWOG (unpublished data). The latter trials, and those cited of cis-platin plus VP-16 as an "alternating combination" de novo (que), cast considerable doubt on the concept that this combination is really non-cross-resistant, at least with CAV.

A new combination with considerable basis in experimental systems was the "BTOC" regimen studied by SWOG (BCNU, thiopeta, vincristine (Onocovin), and cyclophosphamide). Unfortunately, the consistent synergism demonstrated in animal model tumors for combined alkylating agents could not be demonstrated: BTOC and CAV were regimens of equal efficacy in the SWOG randomized trial. Simultaneous combinations of VP-16 and cis-platin with other active drugs are of current interest. Adriamycin and cyclophosphamide were added in the "PACE" combination by Aiwer et al and, in a different combination of the 4 agents, by Klastersky et al for the EORTC. Although high response rates were seen, no obvious improvement in survival was reported in preliminary analyses of this regimen, and its toxicity is probably prohibitive. The combination of cyclophosphamide, vincristine, cis-platin, and VP-16 (COPE) is currently under study within the SWOG.

The only new agent with promising activity as initial treatment is carboplatin (CBDCA), a cisplatin analog that is nonnephrotoxic but more myelosuppressive. Whether it will be more active in combination with VP-16 (or other agents) than the parent compound remains to be seen.

CONCLUSIONS

Several "standard" regimens of chemotherapy, with comparable efficacy for small cell lung cancer presently exist, including CAV, CMC, and CMC plus vincristine. The addition of an active new agent, VP-16, has not been shown to produce survival benefit, although it probably increases the response rate in extensive disease. Maintenance chemotherapy as it has been practiced is probably of little value. Solid evidence is lacking that any drug regimen (including cisplatin plus VP-16) is genuinely non-cross-resistant with the standard combinations, and, possibly for this reason, studies of the Goldie-Coldman hypothesis have not yet been able to validate the concept of alternating effective combinations. Anticoagulation is of no demonstrated value.

Leads to pursue now in chemotherapy involve primarily further exploration of the dose-response hypothesis, especially for cyclophosphamide. Both as an approach for induction and as "consolidation," limited data suggest that such an approach will bear fruit. It may be most logical now to confine the use of very high-dose cyclophosphamide, with or without other agents to patients with limited disease. Autologous marrow infusion is not necessary if systemic irradiation and nitrogenous are not used. It is clear that available drugs
alone, in any dose or schedule, will be insufficient to control disease at the primary site in many patients. Thus, the search must continue for the optimal sequencing and schedule of chemotherapy with the available "local" modalities of radiation therapy and surgery. The hope exists that monoclonal antibodies or some other form of biologic response modification will prove effective at eradicating residual, microscopic foci of potentially multidrug-resistant clones which presumably form the basis for systemic failure in other patients.

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